REMARKS

Claims 1 - 31 are currently pending in the above-identified application. The Examiner has acknowledged Applicants' election with traverse of Group II (claims 1, 2, and 6-17) and the species of a) HPV E7 as the peptide or protein antigen and b) B7-1 as the costimulatory molecule. Further, the restriction requirement has been made final and claims 3 - 5, 9, 10 and 18 - 31 have been withdrawn by the Examiner from consideration as being drawn to non-elected inventions. Claims 1, 2, 6-8, and 11 - 17 therefore have been substantively examined.

By this amendment, the specification has been amended to correct certain typographical and clerical errors. Claims 3 - 5, 9, 10 and 18 - 31 have been canceled without prejudice to Applicants' right to prosecute the subject matter of the claims in a related co-pending application.

The Examiner believes the declaration originally submitted with the instant application under 37 C.F.R. § 1.63 to be defective because the inventors' addresses and post office addresses are not given in the declaration. Applicants respectfully request the Examiner reconsider this objection because the inventors' residence and mailing addresses need not be identified in the oath or declaration if such information is supplied on an application data sheet in accordance with 37 C.F.R. § 1.76. 37 C.F.R. § 1.63(c)(1). Although Applicants believe that all requirements have been met as the application data sheet (ADS) originally submitted with the application identifies the inventors' residence and mailing addresses, to further expedite prosecution of the present application, a newly executed Declaration listing the mailing addresses for the named inventors in provided.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 6-8, and 11-17 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the claims "encompass a method for gene therapy," and asserts that there is insufficient disclosure in the specification for the claimed method. The Examiner, further states that there are "insufficient relevant identifying characteristics disclosed, "believing that the specification as filed does not disclose the treatment of subjects with peptide antigens other than HPV E7 peptide antigen and a non-viral vector encoding a costimulatory molecule other than B7.1.

Applicants traverse the present rejection because the Examiner has not made a *prima facie* case for lack of written description under 35 U.S.C. § 112, first paragraph. Applicants respectfully note that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. MPEP § 2163 (I)(A); *In re Wertheim*, 191 USPQ 90, 97 (CCPA 1976). The Examiner bears the initial burden of coming forward with evidence or reasoning "why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." *Id.*

In the present case the Examiner appears to base the rejection on the assertion that the instant claims "encompass a method of gene therapy". No additional reasoning is provided other than a statement that insufficient relevant identifying characteristics are disclosed. Applicants believe the Examiner has not clearly established the relevance of either assertion under the written description requirement of 35 U.S.C. § 112, first paragraph. The term "gene therapy" as used in the relevant art and by the Examiner in the present Office Action can refer to treatment approaches that are based on different types of genetic material and/or techniques (*e.g.*, use of viral or non-viral vehicles; use of sense or antisense molecules; *in vivo* or *ex vivo* transfection or transduction methods; upregulation or downregulation of a target gene; and the

like). "Gene therapy" therefore can encompass many methods and compositions that do not share characteristics with those defined by the instant claims. Applicants believe that analyzing the claimed method under a general characterization of "gene therapy" is improper under 35 U.S.C. § 112, first paragraph. Instead, the invention for purposes of the written description requirement is "*whatever is now claimed*," *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (emphasis added), and the essential inquiry is whether there is sufficient disclosure such that one of ordinary skill in the art, reading the specification as filed, would understand that the applicant was in possession of the invention *set forth in the claim at issue*, *see id.*

Applicants further note that, in stating the "specification does not disclose treatment of subjects with peptide antigens other than . . . HPV E7 and a non-viral vector encoding a costimulatory other than B7.1," the Examiner appears to have interpreted adequate written description as requiring no less than actual reduction to practice. In this regard, Applicants must respectfully disagree with the Examiner. Adequate written description of the claimed invention may be shown by "*any description* of sufficient, relevant identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163 (II)(A)(3)(a) (emphasis added); *see also Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (U.S. 1998) (stating that "reduction to practice is not necessary in every case").

In light of the above, Applicants respectfully object to the Examiner's consideration only of those species exemplified by an actual reduction to practice in the specification. Relevant identifying characteristics of the peptide and protein antigens comprising one or more T cell epitopes and polynucleotides encoding T cell costimulatory molecules are present in the specification and must be considered in determining whether the written description requirement under 35 U.S.C. § 112, first paragraph, is met. Applicants respectfully direct the Examiner to, for example, page 9, line 6 through page 26, line 31 wherein characteristics for peptide and protein antigens and particular peptides and proteins for use in the present invention are disclosed. Further, the characteristics of co-stimulatory molecules for use

in the present invention are disclosed at, for example, page 27, lines 1 through 30 and throughout the specification.

For the reasons set forth above, Applicants believe that the Examiner has not set forth a *prima facie* case for lack of written description under 35 U.S.C. § 112, first paragraph. The Examiner's mere assertion that there are "insufficient relevant characteristics disclosed," without setting forth specific evidence or reasons that relate directly to the invention as claimed describing why the disclosure in the specification is allegedly insufficient, does not meet the Examiner's evidentiary burden. As indicated above, the Examiner's assertion that the claimed invention "encompasses a method of gene therapy," by virtue of the broad generalization inherent in such a statement, is insufficient to point to an aspect of the claimed invention that has not been described with sufficient particularity. Applicants believe that the Examiner has failed to present any specific evidence or reasons why the present disclosure is inadequate to satisfy the written description requirement under 35 U.S.C. § 112, first paragraph.

Therefore, Applicants respectfully traverse the instant rejection. For the reasons set forth above, Applicants believe that the claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and the Examiner is respectfully requested to reconsider and withdraw the rejection for lack of written description under 35 U.S.C. § 112, first paragraph.

Claims 1, 2, 6-8, and 11-17 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing the claims to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention. The Examiner states that the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims "encompass a method of gene therapy." The Examiner further believes that the state of the art (presumably referring generally to the "gene therapy" art) is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used. The Examiner cites to Nelson *et al.* (Washington Post Jan. 31, 2000 "Earlier Gene Test Deaths Not Reported; NIH Was Unaware of 'Adverse Events'") (herein "Nelson I") and Nelson

et al. (Washington Post, May 25, 2000, page A01) (herein "Nelson II"), to generally allege that "[g]ene therapy has been largely ineffective and has induced mortality." Based on these publications, the Examiner states that there is insufficient guidance in the specification as to how to practice the method of the instant invention. The Examiner believes that undue experimentation would be required to practice the claimed invention.

Applicants traverse the rejection of claims 1, 2, 6-8, and 11-17 under 35 U.S.C. § 112, first paragraph. The Examiner has failed to established a *prima facie* case for non-enablement because general assertions are not a sufficient or reasonable basis for the rejection. To make a rejection for enablement under 35 U.S.C. § 112, first paragraph, the Examiner has the "initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04, *citing In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Enablement is, therefore, presumed:

> ... a specification disclosure which contains a teaching [of how to make and use] the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support....

In re Marzocchi, 169 USPQ 367 (CCPA 1971) (emphasis original).

In the present case, Applicants believe that the Examiner has not presented evidence sufficient to shift the burden under the enablement requirement of 35 U.S.C. § 112, first paragraph. First, as stated above in regard to written description, Applicants respectfully disagree with the Examiner's reliance on a general characterization of the claimed invention as a "method of gene therapy." A determination of enablement under 35 U.S.C. § 112, first paragraph, must be made with respect to the invention that is defined by the claims at issue.

MPEP § 2164. Here, Applicants believe that the term "gene therapy" can refer to treatment approaches that are based on different materials and/or techniques and, thus, may not share characteristics with those materials and/or techniques defined by the instant claims. As, an example the Examiner relies on the cited publications (Nelson I and Nelson II) to support the assertion of non-enablement. The references are cited for the proposition that gene therapy is allegedly "ineffective" and unsafe. Applicants respectfully believe that the Examiner has not established the relevancy of these references to the enablement of the presently claimed invention.

As set forth above, the specification need only enable the invention as *defined by the claims*. MPEP § 2164. In this case, the references cited by the Examiner do not describe the nature of the genetic material (*e.g.*, retroviral, antisense, etc.) nor the particular methods involved in the studies discussed therein. For this reason, the Examiner has not established whether the results of the gene therapy studies discussed in the cited references are applicable to the claimed invention as defined in the present claims. For reasons discussed above, Applicants believe that a mere assertion that the present claims "encompass a method of gene therapy" is insufficient to establish the applicability of these references to the claimed invention. Even assuming, *arguendo*, that such applicability is shown, Nelson I and Nelson II do not demonstrate that the gene therapy treatments caused the "adverse events" mentioned. Accordingly, Applicants respectfully believe that these references are irrelevant and are an improper basis for rejection under 35 U.S.C. § 112, first paragraph. Therefore the Examiner has failed to properly shift the burden of proof to Applicants without further evidence directed to the methods of the claims and the particular disclosure that supports those claims.

Applicants believe that the claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, and the Examiner is respectfully requested to reconsider and withdraw the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 15 stands rejected under 35 U.S.C. § 112, second paragraph, the Examiner believing the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that claim 15 is indefinite in the recitation of "proximal target sites selected from the same, or closely-adjacent ... sites" because "it is not clear what is meant, and closely-adjacent is a relative term."

It is well-established that the dispositive inquiry in the determination of definiteness is whether one of skill in the art would understand the scope of the claim when the claim is read in light of the specification. *See North Am. Vaccine, Inc. v. American Cyanamid Co.*, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993). A claim that uses relative terminology is not rendered invalid for indefiniteness where the specification provides some standard for measuring the degree intended or, if no such standard is provided, if the skilled artisan, in view of the status of the art, would nevertheless be reasonably apprised of the scope of the claimed invention. MPEP § 2173.05(b). Therefore, it is not the technical form of the disclosure that counts but rather the disclosure in the specification itself and in light of the knowledge in the art.

In the present case, the specification discloses a standard for determining "closely-adjacent" sites suitable for administration of the peptide antigen and vector (*see* page 42, lines 25-29, where the specification describes delivery to "closely proximate" sites as "adjacent sites that are structurally or fluidly connected with one another" so as "to allow direct exposure of the same cells"). In view of this disclosed standard, the skilled artisan reading the claim in light of the specification would understand that the phrase, "proximal target sites selected from the same, or closely-adjacent sites," means adjacent sites that are "structurally or fluidly connected with one another" such that the separate administration of the peptide or protein antigen and the non-viral vector allows direct exposure of the same target tissue or cells to both vaccine agents. Further, the specification discloses that "a shared site for delivery of antigen and vector can be a common surface ... of a particular target tissue or cell population, or

an extracellular space, lumen, cavity, or structure that borders, surrounds or infiltrates the target tissue or cell population" (*see* page 42, lines 29-32). Thus, the artisan reading the claim in light of the specification would also understand that determination of "closely-adjacent" sites further includes determination of whether the sites share a common means of access to the target tissue or cells (be it through, for example, "transfer, dissipation or diffusion through a fluid or extracellular matrix," page 42, lines 28 and 29), such that the delivery allows direct exposure to both agents. In addition, because the specification discloses a method for eliciting a immune response according to a "two-signal" model for lymphocyte activation, which involves both the induction of an antigen-specific signal and a secondary, non-antigen specific "co-stimulation" signal on the same immune cells, a meaning for "closely-adjacent" sites as sites which allow exposure of the target tissue to both peptide antigen and the co-stimulatory molecule-encoding vector would be further apparent to the artisan reading the specification.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claim 15 for indefiniteness under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 6-8, and 11-17 stand rejected under 35 U.S.C. § 103(a), the Examiner believing the claims are unpatentable over U.S. Patent No. 5,738,852 in view of WO 98/04705 (document and CAPLUS Accession No. 1998: 106018 summary of document) and Kaufmann *et al.* (*Cell.Immunol.* 1996, 169:246-251). The Examiner asserts, *inter alia*, that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered the viral polypeptide(s), including the HPV E7 polypeptide, and a co-stimulatory molecule, such as B7.1, as a combination of a polypeptide antigen and a polynucleotide encoding the co-stimulatory molecule or vice versa. The Examiner believes that one of ordinary skill in the art would have been motivated to do this because "U.S. Patent No. 5,738,852 discloses that the vaccines can be administered as polynucleotides; WO 98/04705 and

the CAPLUS Accession No. 1998: 106018 teach that the vaccines can be administered either as polynucleotides or as peptides to achieve the common function of eliciting immunity to the viral polypeptide(s)"; and "Kaufman *et al.* teaches that response to HPV E7 polypeptide antigen requires expression of the co-stimulatory molecule B7.1." The Examiner believes that the motivation to combine the elements allegedly disclosed in the cited references arises from an "expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose."

Applicants respectfully traverse the instant rejection. In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must show a motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP § 2143. Applicants believe that the Examiner has not established a motivation or suggestion to combine the cited references in the manner posited in her remarks. The Examiner appears to believe that the motivation to combine the references arises from alleged art-recognized suitability of the recited compositions for an intended purpose. In this regard, and in view of the Examiner's statement that a motivation to combine arises from an "expectation that the prior art elements will perform their expected functions ...," Applicants interpret the apparent basis for the rejection as the existence in the art of an alleged "expectation" that a non-viral vector encoding a co-stimulatory molecule, when coordinately administered to an individual with a polypeptide or protein antigen, would elicit an enhanced antigen-specific immune response. However, the cited references cited do not reasonably convey to the skilled artisan the suitability of co-administration of a non-viral vector for *in vivo* transgene expression of a co-stimulatory molecule to enhance antigen-specific immune response, particularly where the antigen is administered in a different form and at a different site from that of the co-stimulatory molecule (*i.e.*, as a polypeptide rather than as a vector). There is no disclosure or suggestion in the references, for example, that *in vivo* administration of a polypeptide or protein antigen with co-administration at a proximal site of a vector encoding a co-stimulatory molecule will result in sustained gene expression sufficient to achieve the co-stimulatory function of the expressed protein; nor that

such co-stimulatory function can be achieved coordinately so as to increase the immunological function of lymphocytes responding to antigen co-administered as polypeptide, as is shown in the instant specification. Neither US 5,738,852 nor WO 98/04705 demonstrate *in vivo* co-stimulatory function of B7.1 expressed from naked DNA, but rather disclose the administration of an antigen and a co-stimulatory molecule in the same form. For example, US 5,738,852 states "APCs which express a target antigen and are capable of stimulating a T cell response, preferably a CTL response, are created with in vivo or in vitro by the insertion of one or more recombinant polynucleotides containing a sequence encoding at least one costimulatory molecule and at least one target antigen polypeptide". See column 8, lines 41 - 47. Further, WO 98/04705 and the abstract of the application which appears as CAPLUS Accession No. 1998:106018 disclose the combination of an early and late polypeptide, and optionally a co-stimulatory molecule wherein the polypeptides and the co-stimulatory molecule are provided either as polypeptides or polynucleotides encoding the polypeptides. The polypeptides are provided in a single composition. There is no suggestion or disclosure of providing the antigen as a polypeptide form and the administration of the co-stimulatory molecule as a polynucleotide in a separate composition at a proximal site. Furthermore, Kaufmann *et al.* relates to transfection of cervical cancer cell lines *in vitro* with a gene encoding B7.1 and their use as antigen presenting cells in an *in vitro* cytotoxicity assay. Thus, the references themselves do not reasonably evince an expectation in the art that a polypeptide or protein antigen administered proximally to a polynucleotide encoding a co-stimulatory molecule, as recited in the instant claims, will have the necessary *in vivo* co-stimulatory activity; nor has the Examiner cited other art evincing such an expectation.

For the reasons set forth above, Applicants believe that claims 1, 2, 6-8, and 11-17 are non-obvious and that the Examiner has not set forth sufficient evidence demonstrating a motivation to combine the cited references in the manner posited. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 2, 6-8, and 11-17 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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